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EXAMINER	
HAQ, SHAFIQUL	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,857	INOUYE, SATOSHI	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-56* is/are pending in the application.

4a) Of the above claim(s) *3-5,10-12 and 18-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 3-56 are pending of which claims 3-5, 10-12, 18-56 are withdrawn from further consideration as being directed to a non-elected invention (see office action of 6/18/09). Therefore, claims 6-9 and 13-17 are examined on merits.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 6-9 and 13-17 are again rejected under 35 U.S.C. 102(b) as being anticipated by Kurose *et al* (PNAS 1989).

Claim 6 is directed to a composition comprising an apoprotein that is a component of a calcium-binding photoprotein, a coelenteramid or an analog thereof, and a calcium ion or a divalent or trivalent ion that can be substituted for the calcium ion; wherein the coelenteramid remains coordinated inside the apoprotein. The recitation "a fluorescent protein having a chemiluminescent activity" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. Applicant is reminded that a recitation of the intended use of the claimed invention, i.e. "fluorescent protein having a chemiluminescent activity", must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).

With regard to claim 6, Kurose *et al* disclose a fluorescent protein (bFP) having chemiluminescence activity comprising apoaequorin, coelenteramide and calcium ion (page 80, lines 4-16 of left column). Kurose *et al* teach that when Ca^{2+} binds to aequorin, an intramolecular reaction takes place in which coelentrrazine is oxidized to colenteramide by the bound oxygen, yielding as products light, CO_2 and **a blue fluorescent protein and the blue fluorescent protein consists of coelenteramide attached to apoaequorin** (which reads on coelenteramid remains coordinated with the apoprotein) (page 80, lines 10-16 of left column). Kurose *et al* do not mention that the apoaequorin is bound inside the apoprotein but however, since the apoaequorin is the same as that of instant application (see claim 8), the apoaequorin will have the same binding site for coelenteramid (i.e. inside the apoprotein) and thus the attachment of the coelenteramid is inside the apoaequorin.

With regard to claim 7, Kurose *et al* teach that the photoprotein consists of two components: an apoprotein (apoaequorin) and a chromophore and the chromophore is made up of coelenterazine and molecular oxygen. Kurose *et al* further teach that aequorin contains three Ca^{2+} binding sites and binding of calcium to these sites induces a conformational change in the protein, causing an active site to be formed, which caralyzes the oxidation of the bound coelenterazine to coelenteramide (page 80, lines 4-16 of left column), which thus teaches a complex of apoaequorin with a coelenteramide (1:1) and upto three calcium ions bound to the complex as there are three Ca^{2+} binding sites (i.e. 1:3).

With regard to claim 8, Kurose *et al* teach apoaequorin as apoprotein .

With regard to claim 9, the amino acid sequence of SEQ ID NO:1 is an amino acid sequence for apoaequorin from jellyfish *Aequorea Victoria* and the sequence is inherently present in the apoaequorin as disclosed by Kurose *et al* because Kurose *et al* teach apoprotein of jellyfish *Aequorea Victoria*.

With regard to claim 13, Kurose *et al* teach fluorescent protein mutant having chemiluminescence activity comprising mutant apoaequorin wherein at least one of at least two free sulfhydryl group is mutated to serine to disrupt disulfide bonds (see Table 1), coelenteramide and calcium ion (see "RESULTS" section of pages 81-82 and page 83, lines 22-25 of left column).

With regard to claims 14 and 15, Kurose *et al*, as described above, disclose fluorescent protein (bFP) having chemiluminescence activity comprising apoaequorin, coelenteramide and calcium ion (page 80, lines 4-16 of left column) and the coelenteramide reads on the compound of formula (1), when X^2=H, X^1=OH, R^3=H, R^1=an arylated alkyl group substituted with hydroxyl group and R^2=an unsubstituted arylated alkyl group and with regard to claim 17, the compound reads of coelenteramid when R^1= p-hydroxybenzyl group and R^2= benzyl group.

With regard to claim 17, Kurose *et al* teach binding of calcium ion to aequorin, which triggers oxidation of coelenterazine to coelenteramide (page 80, lines 4-16 of left column).

4. Claims 6-9 and 14-17 are again rejected under 35 U.S.C. 102(b) as being anticipated by Inouye *et al* (FEBS Letters 1994).

Claim 6 is directed to a composition comprising an apoprotein that is a component of a calcium-binding photoprotein, a coelenteramid or an analog thereof, and a calcium ion or a divalent or trivalent ion that can be substituted for the calcium ion; wherein the coelenteramid remains coordinated inside the apoprotein.. The recitation "a fluorescent protein having a chemiluminescent activity" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. Applicant is reminded that a recitation of the intended use of the claimed invention, i.e. "fluorescent protein having a chemiluminescent activity", must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).

Inouye *et al* teach that binding of Ca^{2+} to aequorin triggers intramolecular reaction in which coelenterazine is oxidized to coelenteramide, yielding as products a blue fluorescent protein, CO_2 and light, and **the blue fluorescent protein is made up of coelenteramide bound to apoaequorin** (which reads on coelenteramid

remains coordinated with the apoprotein) (page 277, lines 9-21 of left column). Therefore, blue fluorescent protein (bFP) comprises Ca^{2+}, apoaequorin and coelenteramide and the blue fluorescent protein as being having the same composition as the claimed invention would be expected to have chemiluminescent activity. In fact, Inouye *et al* teach that the bFP produces chemiluminescence in the presence of GFP. Inouye *et al* do not mention that the apoaequorin is bound inside the apoprotein but however, since the apoaequorin is the same as that of instant application (see claim 8), the apoaequorin will have the same binding site for coelenteramid (i.e. inside the apoprotein) and thus the attachment of the coelenteramid is inside the apoaequorin.

With regard to claim 8, Inouye *et al* teach apoaequorin as apoprotein (page 277, lines 4-5 of left column)..

With regard to claim 9, the amino acid sequence of SEQ ID NO:1 is an amino acid sequence for apoaequorin from jellyfish *Aequorea Victoria* and the sequence is inherently present in the apoaequorin as disclosed by Inouye *et al* because Inouye *et al* teach apoprotein of jellyfish *Aequorea Victoria*.

With regard to claims 14 and 15, Inouye *et al*, as described above, disclose fluorescent protein (bFP) having chemiluminescence activity comprising apoaequorin, coelenteramide and calcium ion (page 277, lines 9-21 of left column) and the coelenteramide reads on the compound of formula (1), when X^2=H, X^1=OH, R^3=H, R^1=an arylated alkyl group substituted with hydroxyl group and R^2=an unsubstituted arylated alkyl group and with regard to claim 17, the compound reads of coelenteramid when R^1= p-hydroxybenzyl group and R^2= benzyl group.

With regard to claim 17, Inouye *et al* teach binding of calcium ion to aequorin, which triggers oxidation of coelenterazine to coelenteramide (page 80, lines 4-16 of left column).

5. Claims 6-9 and 14-17 are again rejected under 35 U.S.C. 102(b) as being anticipated by Kojima *et al* (Tetrahedron Letters 1997).

Claim 6 is directed to a composition comprising an apoprotein that is a component of a calcium-binding photoprotein, a coelenteramid or an analog thereof, and a calcium ion or a divalent or trivalent ion that can be substituted for the calcium ion; wherein the coelenteramid remains coordinated inside the apoprotein. The recitation "a fluorescent protein having a chemiluminescent activity" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. Applicant is reminded that a recitation of the intended use of the claimed invention, i.e. "fluorescent protein having a chemiluminescent activity", must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).

Kojima *et al* teach that binding of Ca^{2+} to aequorin triggers intramolecular reaction in which coelenterazine is oxidized to coelenteramide, yielding as products **a blue fluorescent protein blue wherein the coelenteramide is bound to apoaequorin** (page 2875 and lines 1-5 on page 2876). Therefore, blue fluorescent

protein (bFP) comprises Ca^{2+}, apoaequorin and coelenteramide and the blue fluorescent protein as being having the same composition as the claimed invention would be expected to have chemiluminescent activity. In fact, Kojima *et al* teach that the bFP produces chemiluminescence in the presence of GFP (lines 3-5 on page 2876). Kojima *et al* do not mention that the apoaequorin is bound inside the apoprotein but however, since the apoaequorin is the same as that of instant application (see claim 8), the apoaequorin will have the same binding site for coelenteramid (i.e. inside the apoprotein) and thus the attachment of the coelenteramid is inside the apoaequorin.

With regard to claim 8, Kojima *et al* teach apoaequorin as apoprotein (page 2875, line 4).

With regard to claim 9, the amino acid sequence of SEQ ID NO:1 is an amino acid sequence for apoaequorin from jellyfish *Aequorea Victoria* and the sequence is inherently present in the apoaequorin as disclosed by Kojima *et al* because Kojima *et al* teach apoprotein of jellyfish *Aequorea Victoria*.

With regard to claims 14 and 15, Kojima *et al*, as described above, disclose fluorescent protein (bFP) having chemiluminescence activity comprising apoaequorin, coelenteramide and calcium ion (page 2875 and lines 1-5 on page 2876) and the structure of coelenteramide (see compound 2 of Scheme 1) reads on the compound of formula (1), when X^2=H, X^1=OH, R^3=H, R^1=an arylated alkyl group substituted with hydroxyl group and R^2=an unsubstituted arylated alkyl group and with regard to claim 17, the compound reads of coelenteramid when R^1= p-hydroxybenzyl group and R^2= benzyl group.

With regard to claim 17, Kojima *et al* teach binding of calcium ion to aequorin, which triggers oxidation of coelenterazine to coelenteramide (Lines 1-5 on page 2876).

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 6-9 and 14-17 are again rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3-8 of U.S. Patent No. 7,396655. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the instant claims (i.e. a composition comprising an apoprotein that is a component of a calcium-binding photoprotein, a coelenteramid or an analog thereof, and a calcium ion or a divalent or trivalent ion that can be substituted for the calcium ion) are fully disclosed in cited claims of US paten '655. As for example, claim 3 of US patent '655 discloses a fluorescent protein comprising an apoprotein of a calcium-binding photoprotein, a coelenteramide or an analog thereof, and a calcium ion or a divalent or trivalent ion that can be substituted for calcium ion and claim 3 also recites proportion of apoprotein, coelenteramide and calcium ion in the composition, which reads on the subject matter of claim 7 of instant application. Since the composition is the same as that of the instant claims, at least an apoprotein in the composition is expected to be in bound form with an coelenteramid in the composition.

As for claims 8-9 of instant application, the limitations are taught in claims 4-5 of US patent '655 and as for claims 14-17, the limitations are taught in claims 6-8 of the US patent '655 .

Response to argument

8. Applicant's arguments filed 9/18/09 have been fully considered and are persuasive to overcome the rejection under 35 USC 112 second paragraph but the arguments are persuasive to overcome the rejections under 35 USC 102 and the rejection under obviousness type double patenting. However, Applicants amendment necessitated modifying the rejections under 35 USC 103 as described in this office action.

Applicants' main argument is that none of the cited references, Kuruse, Inouye and kojima teaches every element of the current claim because at least those references do not teach a fluorescent protein "wherein the coelenteramid remains coordinated inside the apoaequorin".

Applicants' arguments have been fully considered but are not found convincing because the above references clearly teach **"blue fluorescent protein"** wherein **the coelenteramide is bound to apoaequorin** and as described in the rejection this teaching reads on "coelenteramid remains coordinated with the apoprotein" (page 80, lines 10-16 of left column). The references do not mention that the apoaequorin is bound inside the apoprotein but however, since the apoaequorin is the same as that of instant application (see claim 8), the apoaequorin will have the same binding site for coelenteramid (i.e. inside the apoprotein) and thus the attachment/binding of the coelenteramid is inside the apoaequorin as claimed in instant application.

With regard to double patenting rejection, Applicants argued that the method claims '655 patent recites a step of "adding a compound selected from the group consisting of imidazole and Guanidine-HCl to a solution of the luciferase", which is neither recited in, nor obvious over, claims 6-9 and 14-17 of the present application directed to fluorescent proteins and accordingly, the pending claims are therefore patentably distinct from the claims of '655 patent.

Applicants argued that coelenteramid is released from apoaequorin after binding to calcium However, Applicants failed to describe why the presence of at least a single "calcium-apoaequorin-celenteramid" or "apoaequorin-coelenteramid" would not be possible in the composition after addition of calcium. That is a 100% release of coelenteramid from apoaequorin in the composition has not been documented (see page 5, lines 1-5 of specification).

The above arguments have been fully considered but are not found convincing because claims 6-9 and 14-17 are composition/product claims, not method claims and as long at the composition is taught in a prior art reference, it meets the limitation. Note that the "comprising" term in the claims does not exclude other reagents/ingredients in the mixture/composition. As described in the double patenting rejection, the US patent '655 discloses a fluorescent protein comprising an apoprotein of a calcium-binding photoprotein, a coelenteramide or an analog thereof, and a calcium ion or a divalent or trivalent ion that can be substituted for calcium ion and the patent (see claim 3) also recites different proportion of apoprotein, coelenteramide and calcium ion in the composition, which reads on the subject matter of claim 7 of instant application and Applicants failed to clearly address why at least an "apoprotein bound to coelenteramide" is not possible in the composition.

Conclusion

9. Applicants' amendment necessitated new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing

date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicant should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in ipsis verbis, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Primary Examiner, Art Unit 1641